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INCREASED SURVIVAL WITH METHYLPREDNISOLONE POST-TREATMENT IN LE--ETC(U)  
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Project NR 105-516

TECHNICAL REPORT NO. 124

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POST-TREATMENT IN LETHAL ENDOTOXIN SHOCK

Gary L. White, Linda T. Archer,  
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Prepared for Publication

in

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University of Oklahoma Health Sciences Center  
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16 February 1978

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The significance of septic shock in man has been emphasized with McCabe's recent reports estimating approximately 132,000 deaths each year in the United States alone (22). Sepsis, also termed endotoxin shock, is one of the most serious forms of shock (20). The significant changes that are occurring with endotoxin shock show progressive malfunctions in most organ systems, including the heart, liver, lung, kidney and brain, associated with depressed hemodynamics and metabolism (5,16,26). Development of an effective therapy for the treatment of septic shock has often been met with failure due to the inability to completely comprehend the various pathophysiologic mechanisms operative in the experimental animal model (18). Many laboratory studies are difficult to evaluate because various anesthetics have been used (15,28,35), and in unanesthetized animal studies the endotoxin is usually administered by bolus injection rather than by slow infusion (15,28,35). Clinical studies are often hard to assess because controlled data from gravely ill patients in different states of the illness in varying clinical settings are reported (23,35).

Numerous experimental studies employing exogenously administered corticosteroids in the therapy of endotoxin shock have been published, and results vary from negligible effectiveness (14,15) to nearly complete protection (9,24,27,30, 31,36) against the adverse effects of endotoxin. However, the experimental protocols have been greatly restricted, usually consisting of a bolus injection of endotoxin followed, or preceded, by bolus injections of steroid in the anesthetized animal and in many studies the degree of lethality is not stated. Variations in results may be accounted for by the fact that steroids have been used both as a pretreatment (35) as well as post-treatment (15,28) for shock.

Although a recent clinical study has demonstrated statistically significant protection with steroids against the lethal effects of sepsis (32), the value of corticosteroids for the treatment of septic shock still remains a controversial



issue (28,33,35). Suggested benefits of corticosteroid action in the animal model subjected to endotoxin shock include stimulation of gluconeogenesis (19); decreased pulmonary congestion and pathology (28); preservation of integrity of cellular membranes (37); promotion of adequate tissue perfusion (24); protection of the liver during warm ischemia (9); increased blood flow and elevated arterial blood pressure (15,36); increased cardiac output (30); and augmented muscle, skin and bone blood flows (15). Since studies in endotoxin shock have demonstrated hepatosplanchnic pooling of blood, hypoglycemia (4) and depressed gluconeogenesis (12), it would seem that glucocorticoids reported to stimulate gluconeogenesis, promote tissue perfusion and protect the liver from ischemia, should diminish or abolish the adverse effects of endotoxin. Therefore, the glucocorticoid, methylprednisolone sodium succinate (Solu-Medrol, Upjohn Co.; Kalamazoo, Michigan) was chosen in the present study as a therapeutic regimen for the treatment of endotoxin shock in the canine receiving intravenous LD<sub>100</sub> of E. coli endotoxin by either slow infusion or bolus injection.

#### METHODS

Thirty adult mongrel dogs of random sex, selected for freedom of clinical signs of disease, were used in the present study. All dogs were screened for microfilaria of Dirofilaria immitis (heartworms) and eliminated if positive. Animals were treated for intestinal parasites and allowed a stabilization period of 3-6 weeks; only those with leukocyte counts in the range of 8,000 to 22,000/mm<sup>3</sup> and hematocrits exceeding 36% were utilized.

This study was divided into five groups with each group consisting of six dogs. Group I included awake dogs given slow infusions of E. coli endotoxin (LD<sub>100</sub>) (Difco, Detroit) during a 5-hour period with no therapy. Animals in

Group II were also awake and administered slow infusions of endotoxin ( $LD_{100}$ ) during a 5-hour period with methylprednisolone sodium succinate (MP) post-treatment beginning at +15 minutes after initial infusion of endotoxin. The steroid (MP 50 mg/ml sterile water) was given in a bolus injection of 30 mg/kg at +15 minutes, and a maintenance dose was given via slow infusion starting at +90 minutes over a 120-minute period at a dosage of 15 mg/kg. Group III dogs were anesthetized with sodium pentobarbital, 30 mg/kg, and then administered the  $LD_{100}$  dose of endotoxin by slow infusion. This group received MP as administered to Group II. Group IV animals were anesthetized with sodium pentobarbital, then given a bolus injection of endotoxin ( $LD_{100}$ ) and administered MP as in Groups II and III. Group V animals received a bolus injection of endotoxin ( $LD_{100}$ ) after they were anesthetized with sodium pentobarbital but were not treated with methylprednisolone. The  $LD_{100}$  of E. coli endotoxin (mean, 2.25 mg/ml) was established by utilizing the survival results from Groups I and V (non-steroid treated endotoxin-shocked animals) in which all dogs died.

A Longwell indwelling catheter (Beckton-Dickinson; Rutherford, New Jersey) was placed in the external jugular vein of all animals studied and taped in place for collecting blood samples and administering endotoxin and steroid. A special sling was used to support the unanesthetized dogs in a comfortable upright position during the initial 7 hours; afterwards, the dogs were returned to their cages. Dogs living through 7 days post-endotoxin were considered permanent survivors.

Experiments were designed to follow alterations in peripheral white blood cell (WBC) counts, rectal temperature ( $T_R$ ), hematocrit (Hct) and blood glucose concentrations, in both treated and non-treated animals. In all groups glucose, WBC,  $T_R$ , and Hct were measured initially before endotoxin as well as +15 and +30 minutes after endotoxin, then hourly from +60 through +420 minutes. Blood samples were also collected at +24 hours and +7 days post-endotoxin in surviving animals.

Rectal temperatures were obtained using a Tele-Thermometer probe (Yellow Springs Instruments; Yellow Springs, Ohio). Leukocyte counts were measured with a Coulter Z<sub>F</sub> automatic particle counter (Coulter Electronics, Inc.; Hialeah, Fla.). Blood glucose concentrations were determined using a Beckman glucose analyzer (Beckman Instruments, Inc.; Fullerton, Calif.) with an accuracy of  $\pm 3$  mg%. Statistics were carried out utilizing t test for paired or unpaired data.

### RESULTS

Table 1 shows individual changes in hematocrit in dogs receiving LD<sub>100</sub> E. coli endotoxin while Table 3 presents mean values and statistical analysis of the same data. The most marked increases ( $p < 0.02$ ) in hemoconcentration were observed in animals not receiving methylprednisolone (MP) following a slow infusion of endotoxin (Group I, Table 3). Dogs treated with MP after slow infusion of endotoxin (Groups II and III) exhibited significantly lower hematocrit values ( $P < 0.05$ ) when compared with animals administered endotoxin without MP treatment (Groups I and V). Hematocrits also markedly increased ( $p < 0.05$ ) in dogs administered the bolus injections of endotoxin and post-treated with MP (Group IV) compared with animals slow-infused with endotoxin and treated with MP (Group II). Hematocrits remained elevated in two dogs in Group IV that survived through 24 hours but died by 36 hours post-endotoxin administration.

Survival data are shown in Tables 1 and 2. Increased survival rates (83%) were observed in the two groups of animals receiving slow infusions of LD<sub>100</sub> endotoxin and post-treated with MP (Groups II and III). Of particular interest is the fact that anesthesia did not influence survival results. Animals with the most marked increases in hematocrit did not usually survive. All dogs in Group I died when administered LD<sub>100</sub> E. coli endotoxin over a 5-hour infusion period. All six animals in Group IV receiving a bolus injection of LD<sub>100</sub> endotoxin died even



though they were post-treated with methylprednisolone. The mortality rate was 100% for Group V after LD<sub>100</sub> bolus in the absence of treatment with methylprednisolone.

Alterations in blood glucose concentration in individual animals in response to LD<sub>100</sub> endotoxin are arrayed in Table 2 while mean values with statistical evaluations are shown in Table 4. The individual values in Table 2 reveal that hypoglycemia progressively developed in Groups I and V in which methylprednisolone was not administered and in Group IV animals receiving bolus endotoxin with MP treatment. In Groups II, III and IV administered MP a significant hyperglycemia was seen approximately 30 to 120 minutes post-endotoxin ( $p < 0.05$ ) (Table 4). Group V animals given bolus injections of endotoxin but no steroid developed hyperglycemia at 240 to 300 minutes post-endotoxin ( $p < 0.01$ ) compared with all groups treated with MP (Group II, III and IV). Blood glucose values were significantly higher ( $p < 0.05$ ) as late as 7 hours after endotoxin in Group III animals given MP compared with animals in Group I not receiving methylprednisolone.

Changes in rectal temperature are listed in Table 5. The control temperatures for Groups IV and V were significantly higher ( $p < 0.05$ ) than those for Groups I and II, apparently due to random sampling. Groups I through IV showed significant febrile responses after administration of endotoxin by either slow infusion or bolus injection in both awake and anesthetized dogs. In Group V the only significant increase of rectal temperature occurred at 360 minutes with only two dogs surviving at that time.

Table 6 presents alterations in peripheral leukocyte concentration after administration of endotoxin. Endotoxin injection caused a significant leukopenia in all five groups ( $p < 0.05$ ) at 15 through 60 minutes when compared to control values. The levels of leukopenia for Groups IV and V receiving endotoxin by bolus injection were lower ( $p < 0.05$ ) than in the slow-infused groups (Groups I, II and III).

A significant leukocytosis ( $p < 0.01$ ) was observed at 24 hours in Groups II and III in which 83% of all animals survived.

#### DISCUSSION

Corticosteroid therapy in the treatment of septic shock is still a controversial subject among both clinicians and medical scientists (35). Many laboratory studies are difficult to evaluate because they involve either pretreatment (use of drugs prior to administration of endotoxin) or multiple treatment with bolus injections of endotoxin in contrast to slow infusions (15,28,35).

The primary purpose of this study was to determine the effectiveness of intravenous administration of methylprednisolone sodium succinate (MP) as a post-treatment for canine endotoxin shock. Shock was produced in awake and anesthetized dogs via either bolus injections or 5-hour infusions of  $LD_{100}$  *E. coli* endotoxin. Results clearly demonstrate an increased survival (83%) with MP post-treatment alone during slow infusion of endotoxin. In contrast, all dogs post-treated with MP died when endotoxin was administered as a bolus. Schumer's double-blind study of patients in sepsis documented increased survival with methylprednisolone (32) which is corroborated by the present studies using a slow infusion model. Thomas and Brockman found that post-treatment with methylprednisolone did not alter survival results in dogs administered intravenous bolus endotoxin (35). Following injection of MP (30 mg/kg) at 1 and 7 hours after bolus injection of  $LD_{50-60}$  *E. coli* endotoxin, survival time was lengthened (48 hours) in dogs subjected to endotoxin shock (28). Results from the present study clearly indicate that the most appropriate procedure possessing clinical relevance is the endotoxin slow infused model.

Previous work from this laboratory using  $LD_{80}$  endotoxin in dogs with MP post-treatment revealed only a 47% increase in survival rate (15); MP was injected intravenously +15 minutes after endotoxin at a dose of 20 mg/kg body weight with

no maintenance doses of the steroid utilized. The half-life of MP has been reported to be approximately 3-4 hours (8); therefore, in the present study a maintenance dose of 15 mg/kg body weight was infused for a 2-hour period beginning 90 minutes after the onset of endotoxin infusion and 75 minutes following the initial 30 mg/kg injection of methylprednisolone. The additional administration of MP may have influenced survival by maintaining its plasma concentration at effective levels during and following administration of endotoxin.

A controversy currently exists over the use of anesthetics in animal shock models. Data from the present study clearly document that use of sodium pentobarbital (30 mg/kg body weight) as an anesthetic agent does not influence survival results. Both groups of animals receiving MP after slow infusion of LD<sub>100</sub> endotoxin had an 83% survival rate although six dogs were anesthetized and six animals were awake.

Hematocrit increased markedly ( $p < 0.05$ ) in all groups; however, Group II and III animals post-treated with MP showed significantly less hemoconcentration. The degree of hemoconcentration was presumably an important factor in determining mortality. The decreased hematocrits seen in surviving animals could be attributed to the steroid's action in preserving the integrity of cell membranes (37), promotion of tissue perfusion (24), increased blood flow, and elevated blood pressure (15,36). Prager et al has previously demonstrated that dogs given steroids required less fluid to maintain systemic arterial pressure and urine output (28).

Normoglycemia was associated with survival of animals in Groups II and III receiving a lethal slow infusion of endotoxin followed by treatment with methylprednisolone. The presence of normoglycemia suggests a stimulating effect of methylprednisolone on hepatic gluconeogenesis (19) possibly through promotion of adequate hepatic perfusion (9,24). An increased mesenteric blood flow in endotoxin-shocked dogs post-treated with methylprednisolone has been reported (36). In a



study of rabbits subjected to 30-minute portal vein occlusions producing liver ischemia, 90% of the animals died, while with MP post-treatment only 56% died (9). Animals in Groups I, IV and V all became hypoglycemic during this study and all dogs died in these three groups. Hypoglycemia has been previously associated with death in canine endotoxin shock (1,4,18) and in man during septic shock (29). A positive correlation has been previously established between maintained blood glucose levels and survival in dogs subjected to endotoxin shock (18). Therefore, the action of methylprednisolone on the liver may have been an important factor determining survival in the present study.

The early leukopenia observed in all groups after initiation of either slow infusion or bolus injection of endotoxin was similar to previous results reported by this laboratory (17) as well as those of other investigators (2,3,31). The initial leukopenia was more severe in the two groups receiving bolus injections of endotoxin. Mulholland and Cluff reported that endotoxin causes granulocytes to adhere to the capillary endothelial cells and then later leave the circulation and move into the tissue (25). The return of the leukocyte count to near normal or to a leukocytotic state corroborates earlier studies and may be the result of entry of new leukocytes from the bone marrow into the circulation (10,13,17). Leukocytosis has also been reported to occur after corticosteroid injection (6), and this mechanism might account for some degree of the leukocytosis seen in the survivors. The leukocytosis seen in the animals infused with LD<sub>100</sub> endotoxin and treated with steroid was similar to but more marked than that observed in dogs given sublethal endotoxin as previously reported (38,39,40).

Elevated temperatures occurred in all groups except Group V. Although the mechanisms for the pyrogenic response to endotoxin are not clearly identified, studies have shown that the neutrophil can release a pyrogen which will produce

a febrile response in animals administered endotoxin (11). There is also evidence that endotoxin produces fever by direct action upon the brain (10). A recent hypothesized mechanism is that hyperthermia may be due to inhibition of Prostaglandin  $E_2$  catabolism in the hypothalamus (34). Corticosteroids have been reported to reduce leukocyte pyrogen production (7); however, the groups receiving corticosteroid in this study still exhibited fevers. This may have been due to an overwhelming quantity of endotoxin resulting in excessive pyrogen versus anti-pyrogenic activity of the corticosteroid. The absence of an elevated temperature in Group V may be the result of the lethal bolus injections of endotoxin producing a poor tissue perfusion, thus negating any pyrexia from pyrogen release.

#### SUMMARY

The use of corticosteroids has long been intensively studied for the treatment of septic shock; however, there still remains much controversy over their use. This study was designed to determine the therapeutic value of post-treatment with methylprednisolone sodium succinate (MP) in the awake and anesthetized canine receiving  $LD_{100}$  of *E. coli* endotoxin by either intravenous slow infusion or bolus injection. The MP was administered initially at 15 minutes post-endotoxin at a 30 mg/kg body weight dose and then followed at 90 minutes with a maintenance dose of 15 mg/kg by slow infusion over a 120-minute period. It was found that post-treatment with MP produced a significant increase (83%) in survival in dogs receiving  $LD_{100}$  *E. coli* endotoxin (2.25 mg/kg) by slow infusion whether awake or sodium pentobarbital anesthetized. Both the 5-hour infusion and bolus injection of the endotoxin (2.25 mg/kg) produced a 100% mortality with no post-treatment. Post-treatment with the MP did not alter the 100% mortality in the canine bolus-injected endotoxin shock model. Survival was associated with a normoglycemia and stabilized hematocrit, while death was accompanied by hypoglycemia and severe hemoconcentration.

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TABLE 1. CHANGES IN HEMATOCRIT<sup>a</sup> IN DOGS ADMINISTERED AN LD<sub>100</sub> E. COLI<sup>b</sup> ENDOTOXIN

| Dog no.  | Control | Time, minutes |      |      |      |      |      |      |      |      |     | hours |      | Fate  |
|--|---------|---------------|------|------|------|------|------|------|------|------|-----|-------|------|-------|
|  |         | +15           | +30  | +60  | +120 | +180 | +240 | +300 | +360 | +420 | +24 | +7    |      |       |
| Group I: Awake dogs, slow infusion endotoxin <sup>c</sup> - no treatment       |         |               |      |      |      |      |      |      |      |      |     |       |      |       |
| 1  | 48      | 48            | 49   | 53   | 65   | 68   | 70   | 68   | 68   | *    |     |       |      | Died  |
| 2  | 36      | 38            | 50   | 57   | 60   | *    |      |      |      |      |     |       |      | Died  |
| 3  | 49      | 49            | 48   | 53   | 61   | 68   | 64   | 64   | 65   | 63   | **  |       |      | Died  |
| 4  | 40      | 41            | 43   | 54   | 61   | 65   | 75   | *    |      |      |     |       |      | Died  |
| 5  | 49      | 50            | 53   | 59   | 63   | 67   | 69   | 65   | 67   | 72   | **  |       |      | Died  |
| 6  | 47      | 53            | 56   | 57   | 71   | 70   | 67   | 68   | 64   | 68   | **  |       |      | Died  |
| Group II: Awake dogs, slow infusion endotoxin - steroid treatment <sup>d</sup> |         |               |      |      |      |      |      |      |      |      |     |       |      |       |
| 7  | 45      | 45            | 44   | 49   | 51   | 51   | 50   | 49   | 48   | 48   |     | 42    | 39   | Lived |
| 8  | 50      | 48            | 54   | 55   | 58   | 60   | 60   | 52   | 51   | 53   |     | 50    | 49   | Lived |
| 9  | 53      | 55            | 61   | 60   | 63   | 62   | 58   | 56   | 55   | 54   |     | 49    | 51   | Lived |
| 10   | 39      | 41            | 56   | 61   | 72   | 66   | 60   | 54   | 52   | 50   | **  |       |      | Died  |
| 11   | 44      | 51            | 58   | 56   | 55   | 52   | 48   | 47   | 49   | 50   |     | 45    | 46   | Lived |
| 12   | 41      | 49            | 50   | 53   | 47   | 44   | 42   | 42   | 44   | 45   |     | 45    | 35   | Lived |
| Group III: Anesthetized dogs, slow infusion endotoxin - steroid treatment      |         |               |      |      |      |      |      |      |      |      |     |       |      |       |
| 13   | 44.5    | 40            | 43   | 44   | 56   | 55   | 54   | 54   | 49.5 | 50   |     | 57.5  | 43   | Lived |
| 14   | 49      | 44            | 46.5 | 48   | 57   | 55   | 54   | 51   | 50   | 52   |     | 41.5  | 45   | Lived |
| 15   | 42.5    | 38            | 43   | 46   | 50   | 51   | 52   | 55   | 56   | 56   |     | 58    | 37   | Lived |
| 16   | 47      | 43            | 50   | 56   | 61   | 58   | 55   | 54   | 60   | 59   |     | 43    | 39   | Lived |
| 17   | 49      | 45            | 54   | 68.5 | 76   | 70   | 69   | 67   | 67   | 68   | **  | **    |      | Died  |
| 18   | 47      | 46            | 47   | 48   | 48   | 50   | 48   | 47   | 47   | 46   |     | 44    | 39.5 | Lived |

TABLE 1 (Con't.)

| Dog no.   | Control | Time, minutes |      |      |      |      |      |      |      |      |      | hours |     | days |      | Fate |
|---|---------|---------------|------|------|------|------|------|------|------|------|------|-------|-----|------|------|------|
|   |         | +15           | +30  | +60  | +120 | +180 | +240 | +300 | +360 | +420 | +24  | +7    |     |      |      |      |
| Group IV: Anesthetized dogs, bolus injection endotoxin <sup>f</sup> - steroid treatment |         |               |      |      |      |      |      |      |      |      |      |       |     |      |      |      |
| 19  | 40      | 42.5          | 40.5 | 51   | 65   | 63   | 66   | 67   | 71   | *    |      |       |     |      | Died |      |
| 20  | 51.5    | 58.5          | 61   | 69   | 71   | 72   | 73   | 74.5 | *    |      |      |       |     |      | Died |      |
| 21  | 42      | 43            | 43   | 48   | 60   | 62   | 64   | 64   | 65   | 63   | **   | **    |     |      | Died |      |
| 22  | 50      | 55            | 53   | 57   | 62   | 63   | 65   | 63   | 66   | 68   | **   | **    |     |      | Died |      |
| 23  | 47      | 45            | 42   | 48   | 49   | 50   | 49   | 48   | 47   | 47   | 64   | 64    | *** | ***  | Died |      |
| 24  | 50      | 52            | 51.5 | 55.5 | 58   | 62   | 64   | 61   | 60   | 58   | 62.5 | 62.5  | *** | ***  | Died |      |
| Group V: Anesthetized dogs, bolus injection endotoxin - no treatment                    |         |               |      |      |      |      |      |      |      |      |      |       |     |      |      |      |
| 25  | 42      | 41            | 40   | 46   | 48   | 50   | 48   | 46   | 46   | 47   |      |       |     |      | Died |      |
| 26  | 45      | 42            | 42   | 46   | 50   | 55   | 60   | 60   | *    |      |      |       |     |      | Died |      |
| 27  | 42      | 41            | 41.5 | 46   | 46   | 65   | 71   | *    |      |      |      |       |     |      | Died |      |
| 28  | 56      | 51            | 56   | 64   | 66   | 72   | 73   | 70   | 70   | 69   | **   | **    |     |      | Died |      |
| 29  | 48      | 51            | 55   | 53   | 62   | 64   | 65   | 67   | *    |      |      |       |     |      | Died |      |
| 30  | 39      | 48            | 48   | 50   | 52   | 55   | 56   | 57   | *    |      |      |       |     |      | Died |      |

<sup>a</sup>Micro hematocrit in percent<sup>b</sup>LD<sub>100</sub> - mean 2.25 mg/kg *E. coli* endotoxin<sup>c</sup>Slow infusion given intravenously over a 5 hour period<sup>d</sup>Post treated with 30 mg/kg methylprednisolone sodium succinate by bolus injection at 15 minutes after endotoxin injection then a slow infusion of 15 mg/kg methylprednisolone at 90 minutes post-endotoxin for a 120 minute period<sup>e</sup>Anesthetized with sodium pentobarbital 30 mg/kg<sup>f</sup>Bolus injection given intravenously over a 2 minute period

\*Death occurred within 60 minutes of previous sample

\*\*Death occurred between 420 minutes and 24 hours

\*\*\*Death occurred between 24 and 36 hours

TABLE 2. ALTERATIONS IN BLOOD GLUCOSE CONCENTRATION<sup>a</sup> IN DOGS ADMINISTERED AN LD<sub>100</sub><sup>b</sup> OF E. COLI ENDOTOXIN

| Dog no.  | Control | Time, minutes |     |     |      |      |      |      |      |      |     | hours |  | days |       | Fate |
|--|---------|---------------|-----|-----|------|------|------|------|------|------|-----|-------|--|------|-------|------|
|  |         | +15           | +30 | +60 | +120 | +180 | +240 | +300 | +360 | +420 | +24 | +7    |  |      |       |      |
| Group I: Awake dogs, slow infusion endotoxin <sup>c</sup> - no treatment               |         |               |     |     |      |      |      |      |      |      |     |       |  |      |       |      |
| 1  | 100     | 92            | 86  | 136 | 78   | 54   | 56   | 39   | 33   | *    |     |       |  |      | Died  |      |
| 2  | 78      | 87            | 81  | 66  | 40   | *    |      |      |      |      |     |       |  |      | Died  |      |
| 3  | 101     | 88            | 70  | 84  | 67   | 52   | 61   | 54   | 57   | 57   | **  |       |  |      | Died  |      |
| 4  | 90      | 101           | 103 | 116 | 80   | 59   | 39   | *    |      |      |     |       |  |      | Died  |      |
| 5  | 77      | 74            | 79  | 75  | 81   | 65   | 68   | 60   | 67   | 61   | **  |       |  |      | Died  |      |
| 6  | 106     | 95            | 90  | 96  | 104  | 81   | 73   | 67   | 68   | 61   | **  |       |  |      | Died  |      |
| Group II: Awake dogs, slow infusion endotoxin - steroid treatment <sup>d</sup>         |         |               |     |     |      |      |      |      |      |      |     |       |  |      |       |      |
| 7  | 109     | 110           | 165 | 168 | 153  | 99   | 97   | 75   | 78   | 66   | 81  | 112   |  |      | Lived |      |
| 8  | 97      | 98            | 93  | 136 | 123  | 111  | 109  | 90   | 96   | 107  | 140 | 120   |  |      | Lived |      |
| 9  | 104     | 113           | 144 | 132 | 144  | 118  | 120  | 112  | 136  | 107  | 120 | 98    |  |      | Lived |      |
| 10   | 92      | 87            | 108 | 106 | 71   | 55   | 51   | 41   | 29   | 23   | **  |       |  |      | Died  |      |
| 11   | 107     | 95            | 91  | 120 | 103  | 106  | 80   | 91   | 75   | 88   | 108 | 101   |  |      | Lived |      |
| 12   | 103     | 100           | 109 | 110 | 93   | 80   | 100  | 79   | 80   | 85   | 74  | 103   |  |      | Lived |      |
| Group III: Anesthetized dogs, <sup>e</sup> slow infusion endotoxin - steroid treatment |         |               |     |     |      |      |      |      |      |      |     |       |  |      |       |      |
| 13   | 89      | 101           | 180 | 122 | 142  | 106  | 87   | 76   | 58   | 58   | 98  | 88    |  |      | Lived |      |
| 14   | 94      | 108           | 185 | 205 | 144  | 117  | 111  | 97   | 94   | 90   | 103 | 110   |  |      | Lived |      |
| 15   | 96      | 99            | 130 | 104 | 128  | 113  | 115  | 105  | 104  | 115  | 102 | 109   |  |      | Lived |      |
| 16   | 82      | 93            | 130 | 131 | 94   | 80   | 83   | 79   | 83   | 83   | 154 | 96    |  |      | Lived |      |
| 17   | 102     | 106           | 127 | 93  | 94   | 106  | 140  | 109  | 121  | 101  | **  |       |  |      | Died  |      |
| 18   | 91      | 96            | 119 | 97  | 105  | 92   | 80   | 75   | 73   | 82   | 85  | 96    |  |      | Lived |      |



TABLE 2 (Con't.)

| Dog no.   | Control | Time, minutes |     |     |      |      |      |      |      |      |     | hours |     | Fate |
|---|---------|---------------|-----|-----|------|------|------|------|------|------|-----|-------|-----|------|
|   |         | +15           | +30 | +60 | +120 | +180 | +240 | +300 | +360 | +420 | +24 | +7    |     |      |
| Group IV: Anesthetized dogs, bolus injection endotoxin <sup>f</sup> - steroid treatment |         |               |     |     |      |      |      |      |      |      |     |       |     |      |
| 19  | 99      | 104           | 145 | 156 | 124  | 90   | 80   | 43   | 56   | *    |     |       |     | Died |
| 20  | 91      | 115           | 105 | 107 | 75   | 77   | 89   | 92   | *    |      |     |       |     | Died |
| 21  | 84      | 142           | 145 | 173 | 102  | 65   | 57   | 56   | 48   | 50   | **  |       |     | Died |
| 22  | 89      | 126           | 104 | 207 | 164  | 109  | 99   | 85   | 85   | 79   | **  |       |     | Died |
| 23  | 108     | 140           | 103 | 137 | 123  | 94   | 91   | 82   | 67   | 65   | 78  | ***   | *** | Died |
| 24  | 100     | 134           | 141 | 158 | 126  | 91   | 89   | 85   | 98   | 79   | 38  | ***   | *** | Died |
| Group V: Anesthetized dogs, bolus injection endotoxin - no treatment                    |         |               |     |     |      |      |      |      |      |      |     |       |     |      |
| 25  | 98      | 179           | 146 | 119 | 82   | 48   | 49   | 44   | 40   | 60   | **  |       |     | Died |
| 26  | 80      | 123           | 98  | 84  | 84   | 60   | 38   | 35   | *    |      |     |       |     | Died |
| 27  | 97      | 126           | 140 | 101 | 101  | 48   | 50   | *    |      |      |     |       |     | Died |
| 28  | 85      | 85            | 89  | 102 | 104  | 65   | 66   | 53   | 68   | 63   | **  |       |     | Died |
| 29  | 92      | 115           | 105 | 142 | 94   | 81   | 51   | 25   | *    |      |     |       |     | Died |
| 30  | 106     | 137           | 83  | 100 | 93   | 62   | 33   | 15   | *    |      |     |       |     | Died |

<sup>a</sup>Blood glucose in mgm percent<sup>b</sup>LD<sub>100</sub> - mean 2.25 mg/kg *E. coli* endotoxin<sup>c</sup>Slow infusion given intravenously over a 5 hour period<sup>d</sup>post treated with 30 mg/kg methylprednisolone sodium succinate by bolus injection at 15 minutes after endotoxin injection then a slow infusion of 15 mg/kg methylprednisolone at 90 minutes post-endotoxin for a 120 minute period<sup>e</sup>Anesthetized with sodium pentobarbital 30 mg/kg<sup>f</sup>Bolus injection given intravenously over a 2 minute period

\*Death occurred within 60 minutes of previous sample

\*\*Death occurred between 420 minutes and 24 hours

\*\*\*Death occurred between 24 and 36 hours

TABLE 3. ALTERATIONS IN HEMATOCRIT (%) IN DOGS ADMINISTERED ENDOTOXIN (MEAN  $\pm$  SE)<sup>a</sup>

|                         | Time, minutes |       |       |       |       |       |       |       |        |        | hours |       | days |
|-------------------------|---------------|-------|-------|-------|-------|-------|-------|-------|--------|--------|-------|-------|------|
|                         | Control       | +15   | +30   | +60   | +120  | +180  | +240  | +300  | +360   | +420   | +24   | +7    |      |
|                         |               |       |       |       |       |       |       |       |        |        |       | +7    |      |
| Group I <sup>b</sup>    | 45(2)         | 47(2) | 50(2) | 56(1) | 64(2) | 68(1) | 69(2) | 66(1) | 66(1)  | 68(3)  | f     | f     |      |
| Group II <sub>pd</sub>  | 45(2)         | 48(2) | 54(3) | 56(2) | 58(4) | 56(3) | 53(3) | 50(2) | 50(2)  | 50(1)  | 46(2) | 44(3) |      |
|                         |               |       |       |       |       | .02   | .005  | .001  | .001   | .001   |       |       |      |
| Group III <sub>pd</sub> | 47(1)         | 43(1) | 47(2) | 52(4) | 58(4) | 57(3) | 55(3) | 55(3) | 55(3)  | 55(3)  | 49(4) | 41(1) |      |
|                         |               |       |       |       |       | .01   | .005  | .02   | .025   | .05    |       |       |      |
| Group IV <sub>pe</sub>  | 47(2)         | 49(2) | 49(3) | 55(3) | 61(3) | 62(3) | 64(3) | 63(4) | 62(4)  | 59(4)  | 63(1) | f     |      |
|                         |               |       |       |       |       |       | .05   | .02   | .02    | .05    | .005  |       |      |
| Group V <sub>pd</sub>   | 45(3)         | 46(2) | 47(3) | 51(3) | 54(3) | 60(3) | 62(4) | 60(4) | 58(12) | 58(11) | f     | f     |      |
|                         |               |       |       |       | .05   |       |       |       |        |        |       |       |      |

<sup>a</sup> Total of 30 dogs, 6 in each group. All groups were injected with LD<sub>100</sub> (mean 2.25 mg/kg) *E. coli* endotoxin

<sup>b</sup> Group I: awake dogs, slow infusion endotoxin - no treatment; Group II: awake dogs, slow infusion endotoxin - methylprednisolone post-treatment; Group III: anesthetized dogs, slow infusion endotoxin - methylprednisolone post-treatment; Group IV: anesthetized dogs, bolus injection endotoxin - methylprednisolone post-treatment; Group V: anesthetized dogs, bolus endotoxin injection - no treatment (see Methods for details)

<sup>c</sup> Initial measurement for each dog before endotoxin

<sup>d</sup> p = unpaired comparison to Group I

<sup>e</sup> p = unpaired comparison to Group II

<sup>f</sup> 6 of 6 animals died

TABLE 4. CHANGES IN BLOOD GLUCOSE CONCENTRATIONS (MG%) IN DOGS ADMINISTERED ENDOTOXIN (MEAN  $\pm$  SE)<sup>a</sup>

|                             | Control    | Time, minutes      |                     |                    |                    |                    |                    |                   |                  |                  |  | hours       |            | days |
|-----------------------------|------------|--------------------|---------------------|--------------------|--------------------|--------------------|--------------------|-------------------|------------------|------------------|--|-------------|------------|------|
|                             |            | +15                | +30                 | +60                | +120               | +180               | +240               | +300              | +360             | +420             |  | +24         | +7         |      |
|                             |            |                    |                     |                    |                    |                    |                    |                   |                  |                  |  |             |            |      |
| Group I <sup>b</sup>        | 92<br>(5)  | 90<br>(4)          | 85<br>(5)           | 96<br>(11)         | 75<br>(9)          | 62<br>(5)          | 59<br>(6)          | 55<br>(6)         | 56<br>(8)        | 60<br>(1)        |  | e           | e          |      |
| Group II <sup>d</sup><br>p  | 102<br>(3) | 101<br>(4)         | 118<br>(12)<br>.05  | 129<br>(9)<br>.05  | 115<br>(9)<br>.05  | 95<br>(13)<br>.02  | 93<br>(10)<br>.025 | 81<br>(10)        | 82<br>(14)       | 79<br>(13)       |  | 105<br>(12) | 107<br>(4) |      |
| Group III <sup>d</sup><br>p | 92<br>(3)  | 101<br>(2)<br>.05  | 145<br>(12)<br>.001 | 125<br>(17)        | 118<br>(9)<br>.01  | 102<br>(6)<br>.001 | 103<br>(10)<br>.01 | 90<br>(6)<br>.005 | 89<br>(9)<br>.05 | 88<br>(8)<br>.05 |  | 108<br>(12) | 100<br>(4) |      |
| Group IV <sup>d</sup><br>p  | 95<br>(4)  | 127<br>(6)<br>.001 | 124<br>(9)<br>.005  | 156<br>(14)<br>.01 | 119<br>(12)<br>.02 | 88<br>(6)          | 84<br>(6)<br>.02   | 74<br>(8)         | 71<br>(9)        | 68<br>(7)        |  | 58<br>(20)  | e          |      |
| Group V <sup>d</sup><br>p   | 93<br>(4)  | 128<br>(13)<br>.02 | 110<br>(11)         | 108<br>(8)         | 93<br>(4)          | 61<br>(5)          | 48<br>(5)          | 34<br>(7)         | 54<br>(14)       | 62<br>(2)        |  | e           | e          |      |

a,b,c See Table 3

d p = unpaired comparison to Group I

e 6 of 6 animals died



TABLE 5. RESPONSES IN RECTAL TEMPERATURE ( $^{\circ}\text{C}$ ) IN DOGS ADMINISTERED ENDOTOXIN (MEAN  $\pm$  SE)<sup>a</sup>

|                      | Control      | Time, minutes |              |              |              |              |              |              |              |              |  | hours        |              | days         |
|----------------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--|--------------|--------------|--------------|
|                      |              | +15           | +30          | +60          | +120         | +180         | +240         | +300         | +360         | +420         |  | +24          |              | +7           |
| Group I <sup>b</sup> | 37.8<br>(.1) | 38.2<br>(.1)  | 38.6<br>(.2) | 38.9<br>(.2) | 39.2<br>(.5) | 39.7<br>(.3) | 39.8<br>(.2) | 39.7<br>(.3) | 39.5<br>(.3) | 39.2<br>(.5) |  | e            | e            | e            |
| p <sup>d</sup>       |              | .05           | .005         | .001         | .025         | .005         | .001         | .01          | .01          |              |  |              |              |              |
| Group II             | 37.8<br>(.1) | 38.8<br>(.2)  | 38.9<br>(.2) | 39.0<br>(.3) | 38.8<br>(.4) | 38.9<br>(.4) | 39.3<br>(.4) | 39.2<br>(.4) | 38.9<br>(.4) | 38.7<br>(.4) |  | f            | f            | f            |
| p <sup>d</sup>       |              | .005          | .005         | .02          |              | .05          | .02          | .025         | .05          | .05          |  |              |              |              |
| Group III            | 38.0<br>(.1) | 38.5<br>(.1)  | 38.8<br>(.2) | 38.8<br>(.2) | 39.0<br>(.2) | 39.1<br>(.3) | 39.1<br>(.3) | 39.3<br>(.4) | 39.6<br>(.5) | 39.7<br>(.4) |  | 38.3<br>(.3) | 37.9<br>(.2) | 37.9<br>(.2) |
| p <sup>d</sup>       |              | .05           | .01          | .02          | .005         | .025         | .05          | .05          | .025         | .02          |  |              |              |              |
| Group IV             | 38.1<br>(.0) | 38.8<br>(.2)  | 39.0<br>(.2) | 39.1<br>(.2) | 39.3<br>(.4) | 39.4<br>(.5) | 39.7<br>(.6) | 39.9<br>(.6) | 39.8<br>(.8) | 39.6<br>(.7) |  | 38.1<br>(.3) | e            | e            |
| p <sup>d</sup>       |              | .05           | .02          | .01          | .05          | .05          |              | .05          |              |              |  |              |              |              |
| Group V              | 38.3<br>(.1) | 38.3<br>(.2)  | 37.8<br>(.4) | 38.1<br>(.3) | 37.9<br>(.3) | 38.1<br>(.5) | 38.3<br>(.6) | 38.6<br>(.7) | 39.9<br>(.4) | 39.7<br>(.5) |  | e            | e            | e            |
| p <sup>d</sup>       |              |               |              |              |              |              |              |              | .025         |              |  |              |              |              |

a,b,c See Table 3

d p = paired comparison to Control values

e 6 of 6 animals died

f 5 of 6 animals lived through 7 days but rectal temperature was not measured

TABLE 6. VARIATIONS IN LEUKOCYTE COUNTS (/mm<sup>3</sup>) IN DOGS ADMINISTERED ENDOTOXIN (MEAN  $\pm$  SE)<sup>a</sup>

|  | Control         | Time, minutes          |                        |                        |                        |                 |                       |                        |                 |                 |  | hours                   |                 |  |
|--|-----------------|------------------------|------------------------|------------------------|------------------------|-----------------|-----------------------|------------------------|-----------------|-----------------|--|-------------------------|-----------------|--|
|  |                 | +15                    | +30                    | +60                    | +120                   | +180            | +240                  | +300                   | +360            | +420            |  | +24                     | +7              |  |
| Group I <sup>b</sup><br>p <sup>d</sup> | 12800<br>(1700) | 9600<br>(2500)<br>.05  | 5100<br>(500)<br>.01   | 6000<br>(500)<br>.005  | 7900<br>(1500)         | 8800<br>(2200)  | 8600<br>(1900)        | 14600<br>(4800)        | 13900<br>(3300) | 12900<br>(5900) |  | e                       | e               |  |
| Group II<br>p <sup>d</sup>             | 15500<br>(1400) | 6700<br>(1900)<br>.001 | 8700<br>(1900)<br>.005 | 7000<br>(1000)<br>.005 | 7500<br>(1500)<br>.005 | 10200<br>(2100) | 9000<br>(1800)<br>.01 | 14500<br>(2800)        | 17100<br>(4000) | 16300<br>(2700) |  | 41300<br>(6200)<br>.01  | 19700<br>(3200) |  |
| Group III<br>p <sup>d</sup>            | 12600<br>(800)  | 8400<br>(1200)<br>.01  | 5200<br>(900)<br>.001  | 4800<br>(900)<br>.001  | 5100<br>(1000)<br>.005 | 10100<br>(2300) | 7300<br>(1800)<br>.05 | 13500<br>(3900)        | 16800<br>(4200) | 19500<br>(4500) |  | 54600<br>(9500)<br>.001 | 20600<br>(6100) |  |
| Group IV<br>p <sup>d</sup>             | 13500<br>(900)  | 2900<br>(400)<br>.001  | 3900<br>(500)<br>.001  | 4800<br>(300)<br>.001  | 7000<br>(600)<br>.005  | 13000<br>(1100) | 12800<br>(1900)       | 21600<br>(2800)<br>.05 | 19500<br>(3100) | 17400<br>(3500) |  | 20600<br>(6700)         | e               |  |
| Group V<br>p <sup>d</sup>              | 14500<br>(2600) | 2400<br>(200)<br>.005  | 3800<br>(400)<br>.01   | 5400<br>(800)<br>.01   | 7500<br>(900)          | 9600<br>(500)   | 10700<br>(2200)       | 11400<br>(2300)        | 12500<br>(1100) | 13800<br>(2400) |  | e                       | e               |  |

a,b,c See Table 3

d p = paired comparison to Control values

e 6 of 6 animals died

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| <p>The use of corticosteroids has long been intensively studied for the treatment of septic shock; however, there still remains much controversy over their use. This study was designed to determine the therapeutic value of post-treatment with methylprednisolone sodium succinate (MP) in the awake and anesthetized canine receiving LD<sub>100</sub> of <i>E. coli</i> endotoxin by either intravenous slow infusion or bolus injection. The MP was administered initially at 15 minutes post-endotoxin at a 30 mg/kg body weight dose and then followed at 90 minutes with a maintenance dose of 15 mg/kg by slow infusion over a 120-minute period. It was found that post-treatment with MP produced a significant increase (83%) in survival in dogs receiving LD<sub>100</sub> <i>E. coli</i> endotoxin (2.25 mg/kg) by slow infusion whether awake or sodium pentobarbital anesthetized. Both the 5-hour infusion and bolus injection of the endotoxin (2.25 mg/kg) produced a 100% mortality with no post-treatment. Post-treatment with the MP did not alter the 100% mortality in the canine bolus-injected endotoxin shock model. Survival was associated with a normoglycemia and stabilized hematocrit, while death was accompanied by hypoglycemia and severe hemoconcentration.</p> |  |   |                 |

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